American Journal of Medical Genetics 64:556–562 (1996)

A New Observation of Two Cases of Acrofacial Dysostosis Type Genée-Wiedemann in a Family—Remarks on the Mode of Inheritance: Report on Two Sibs*

Luitgard Neumann, Jörg Pelz, and Jürgen Kunze
Institute of Human Genetics and University Childrens Hospital, Humboldt-University of Berlin, Berlin, Germany

We report on a Yugloslavian sibpair with postaxial acrofacial dysostosis type Genée-Wiedemann with some novel signs which broaden the spectrum of this syndrome. The manifestations of the present cases are compared with those of the previously described patients. Life expectancy, change of symptoms over time, and the mode of inheritance are discussed. © 1996 Wiley-Liss, Inc.

KEY WORDS: Genée-Wiedemann syndrome, sibs, postaxial acrofacial dysostosis (POADS), Miller syndrome, mode of inheritance

INTRODUCTION

The Genée-Wiedemann-syndrome, also known as Miller syndrome or postaxial acrofacial dysostosis (POADS), is a rare, well-defined malformation syndrome. As recently shown by Opitz [1987] and Opitz et al. [1993], it seems to be likely that acrofacial dysostosis (AFD) is a polytopic field defect arising during blastogenesis. Up to now there are 26 publications on AFD (35 cases: 19 sporadic and 8 familial) from 10 different countries in Europe, North, and South America. We report a further observation of a sibpair who demonstrates some additional, so far undescribed, signs which broaden the phenotypic spectrum of AFD.

CLINICAL REPORTS

Our patients were a similarly affected pair of sibs, a 13-year-old boy and a 19-year-old young woman. They were the second and the fourth of four children born to nonconsanguineous, healthy parents of Yugoslavian nationality with unremarkable family history.

The following facial abnormalities were observed (Fig. 1a–d): Upward slant of palpebral fissures, blepharophimosis, lateral lower lid ectropion, scarce medial eyelashes; abnormal helices; hypoplastic malar and mandibular bones; conical teeth; and small, median cleft palate were present in both sibs. Limb anomalies included bilateral hypoplasia of the fifth digit (only two phalanges), malposition of the thumbs, and bilateral absence of the fifth toes (Fig. 1e–h). Accessory nipples were observed in the girl. The boy had a small penis and cryptorchidism. Their intelligence was not affected and they had no difficulties while attending regular school in their country. Chromosomes studied on peripheral lymphocytes were normal (46,XX, 46,XY).

Roentgenograms showed the fusion of the capitae and hamae, a flattened joint surface at the proximal joint of digit 1, and a huge apophysis of both olecranons in the girl (Fig. 2a). In the boy (Fig. 2b), partial fusion of the fourth and fifth metacarpals was seen; fusion of the capitae and hamae was present only on the left side; furthermore, short thumbs with proximal joints in subluxation position and flattened joint surfaces were found. Additional radioulnar synostosis and slight bowing of both radii was found in the boy.

The metacarpophalangeal pattern profiles are shown in Figure 3; the standards for the calculation were taken from Poznanski [1974]. Although the levels of the patterns are different the patterns themselves are relative confluent, if one takes into account that the fifth metacarpals in both patients and the proximal phalanx in the female are missing. The correlation (r) calculated for the 17 bones which are present in both sibs is 0.50. The fifth middle phalanx is the most striking. It is disproportionally large compared with the other middle phalanges (>2 S.D.).

DISCUSSION

In Table I the main clinical data of patients with POADS during the last 45 years (including the present

Received for publication August 7, 1995; revision received December 1, 1995.

Address reprint requests to Dr. Jürgen Kunze, Virchow-Klinikum, Humboldt-University, Children's Hospital and Institute of Human Genetics, Augustenburger Platz 1, D-13353 Berlin, Germany.

*This work is dedicated to Professor Dr. H.-R. Wiedemann on the occasion of his 80th birthday.

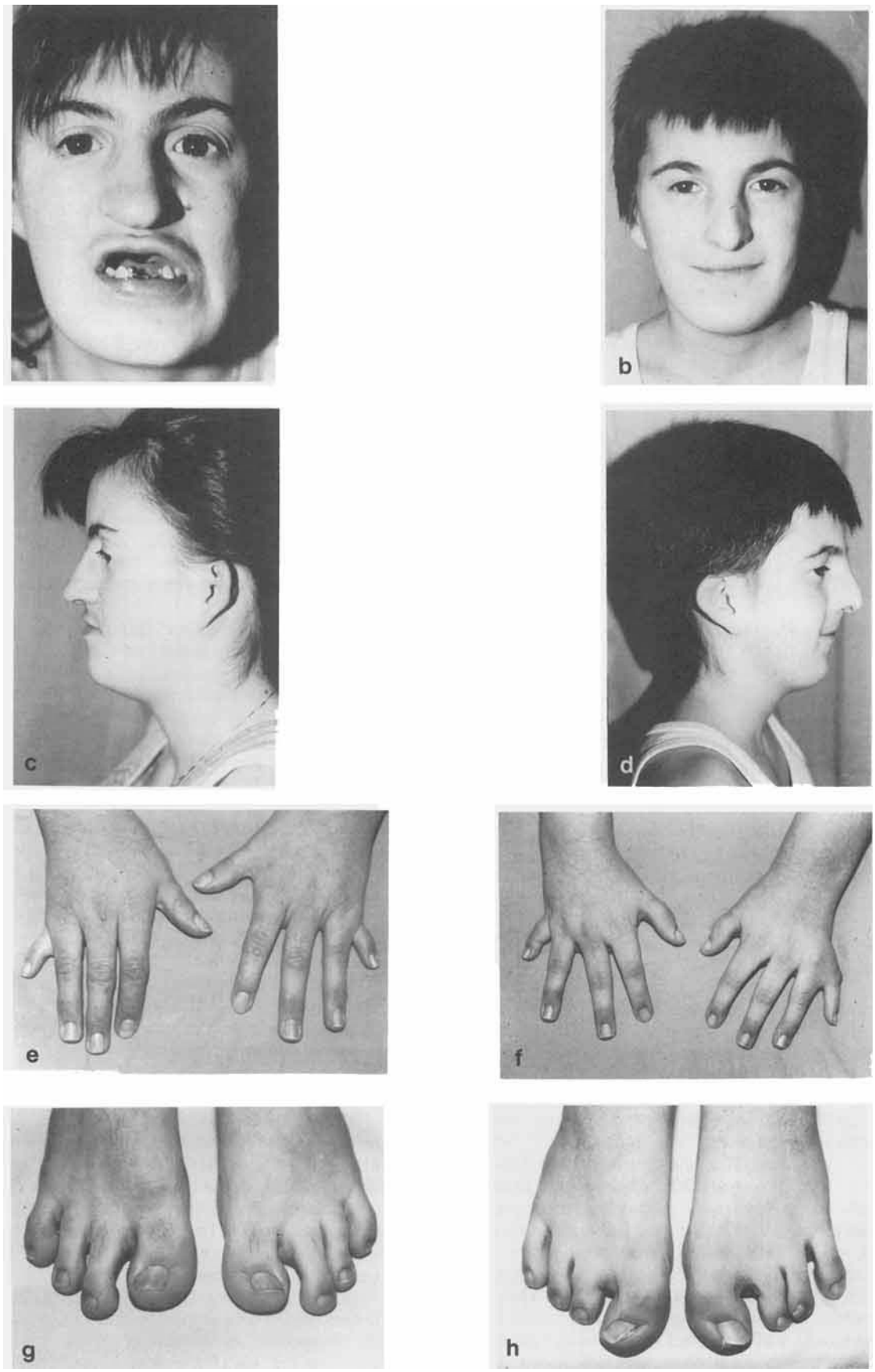

Fig. 1. Phenotypic traits of our patients (a, c, e, g: female patient; b, d, f, h: male patient). Facial appearance of our patients (**a, b**). Note the upward slant of palpebral fissures, blepharophimosis, lateral lid ectropion, scarce medial eyelashes, conical teeth in the girl. Lateral view of the patients (**c, d**) gives evidence of hypoplastic molar and mandibular bones and abnormal helices. Hands of our patients (**e, f**), demonstrating bilateral hypoplasia of the 5th digits and malposition of the thumbs. Feet of the patients (**g, h**) showing absent 5th ray.

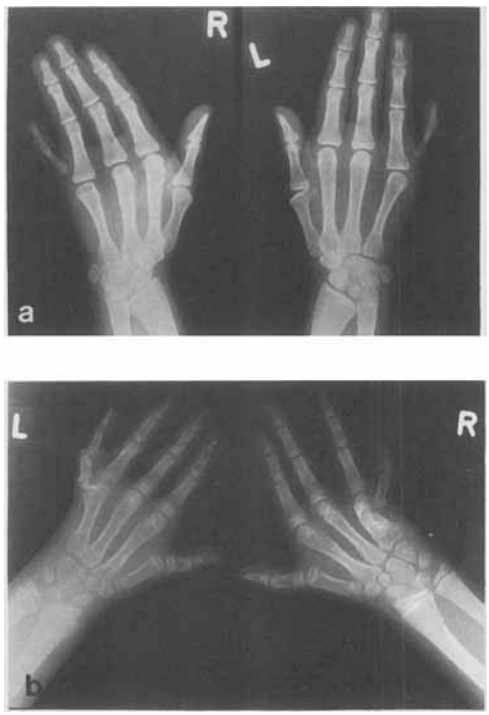

Fig. 2. Roentgenograms of the hands of the girl (**a**) and the boy (**b**).

ones) are listed. We distinguish the sporadic and the familial cases and register only those cases that reported a specific finding as present or absent. The first number indicates a trait as present, the second number includes the cases where the trait was mentioned at all, present or absent. Therefore the second number is sometimes higher than the first one.

Not included in Table I are one female and one male patient described as stillborn cases [Poisonnier et al., 1983; Rodríguez and Palácios, 1990]; a further lethal case [Brunoni et al., 1987, discussed in Opitz et al., 1993] was excluded because if it belongs to AFD at all, it is an atypical case; a male fetus terminated at 22 weeks of gestation reported by Medeira and Donnai [1994] that showed POADS with severe vertebral segmentation defects; and a 4-week-old girl with shortness of limbs without exact clinical description [Richards, 1987].

The pattern of anomalies represented by our patients characterizes the nosologic group of AFD with postaxial involvement confirming the diagnosis of Genée-Wiedemann syndrome. Although postaxial defects are the leading findings, variable degrees of preaxial involvement, as in our male patient, are frequently present. Gorlin et al. [1990] listed conical teeth as a component of POADS but they referred to a case [Allanson and McGillivray, 1985], which is apparently not POADS. Therefore the present case is the first documentation of conical teeth in this syndrome. Blepharophimosis was observed in both of our patients. Up to now this was found in three sporadic cases. Extra nipples were observed only in our female patient, while genital anomalies occurred only in the male.

Neuropsychological aspects are summarized in Table II. In most cases reported, neuropsychological development was described as normal. This is also true of our cases. In all cases of Genée-Wiedemann with some disturbance of neuropsychological development, additional handicaps or later improvements of intellectual functions was reported. One of the sporadic cases [Hauss-Albert and Passarge, 1988] had, in addition, microcephaly, seizures, and profound mental retardation. There may have been secondary brain damage [explained by Opitz et al., 1993]. Delayed mental development is described in the case of Barbuti et al. [1989] with cerebral atrophy. In the sibs of Ogilvy-Stuart and Parsons [1991], there was some developmental delay, which could be explained by physical problems (corneal ulcers and intestinal operations) with early and prolonged hospitalisation. In two cases, intellectual functioning improved markedly with age. In the case of Wiedemann [1973], mental retardation was described in a nearly 3-year-old boy. At the age of 20, a learning disability remained (Meinecke, 1993, personal communication). In the case of Chrzanowska et al. [1989] and Chrzanowska and Fryns [1993a,b], psychomotor retardation was noted in infancy and early childhood. At age 7 years the patient attended a normal school.

There has not yet been enough time to decide whether life expectancy is limited for POADS patients, although some observations have reported data on early death. One female infant of the familial cases died on day 14 because of respiratory distress [Giannotti et al., 1992]. The twin brothers described by Chrzanowska and Fryns [1992] died shortly after birth, one of respiratory distress and the other one with acrania-anencephaly. The severe neural tube defect with the consequence of a fatal course was explained by the authors as possibly related to the twinning process.

The Genée-Wiedemann syndrome is considered an autosomal recessive trait. This assumption is mainly based on the observation of several families in which sibs were affected; the present study adds a new familial case. However, we doubt that the evidence for this form of inheritance is sufficient yet. All pedigrees taken together show minor inconsistencies with what would be expected, if the mode of inheritance is a pure autosomal recessive one.

Rarity of Consanguinity

Cases of the Genée-Wiedemann syndrome should not be missed due to their striking and characteristic anomalies. Since they have been observed only rarely in different countries with good clinical genetic services, sufficient registration of malformations, and a high number of births, the syndrome seems to be very rare with a prevalence at birth of probably less than 10^{-6}, i.e., the gene frequency is less than 10^{-3}. In such rare recessive disorders, the parents of affected individuals tend to be consanguineous in a significant percentage. According to formulas given by Dahlberg [1947] $C = (a(1 + 15q))/(a + 16q - aq)$, where C is the frequency of first-cousin marriages among the parents of children with any particular autosomal recessive dis-

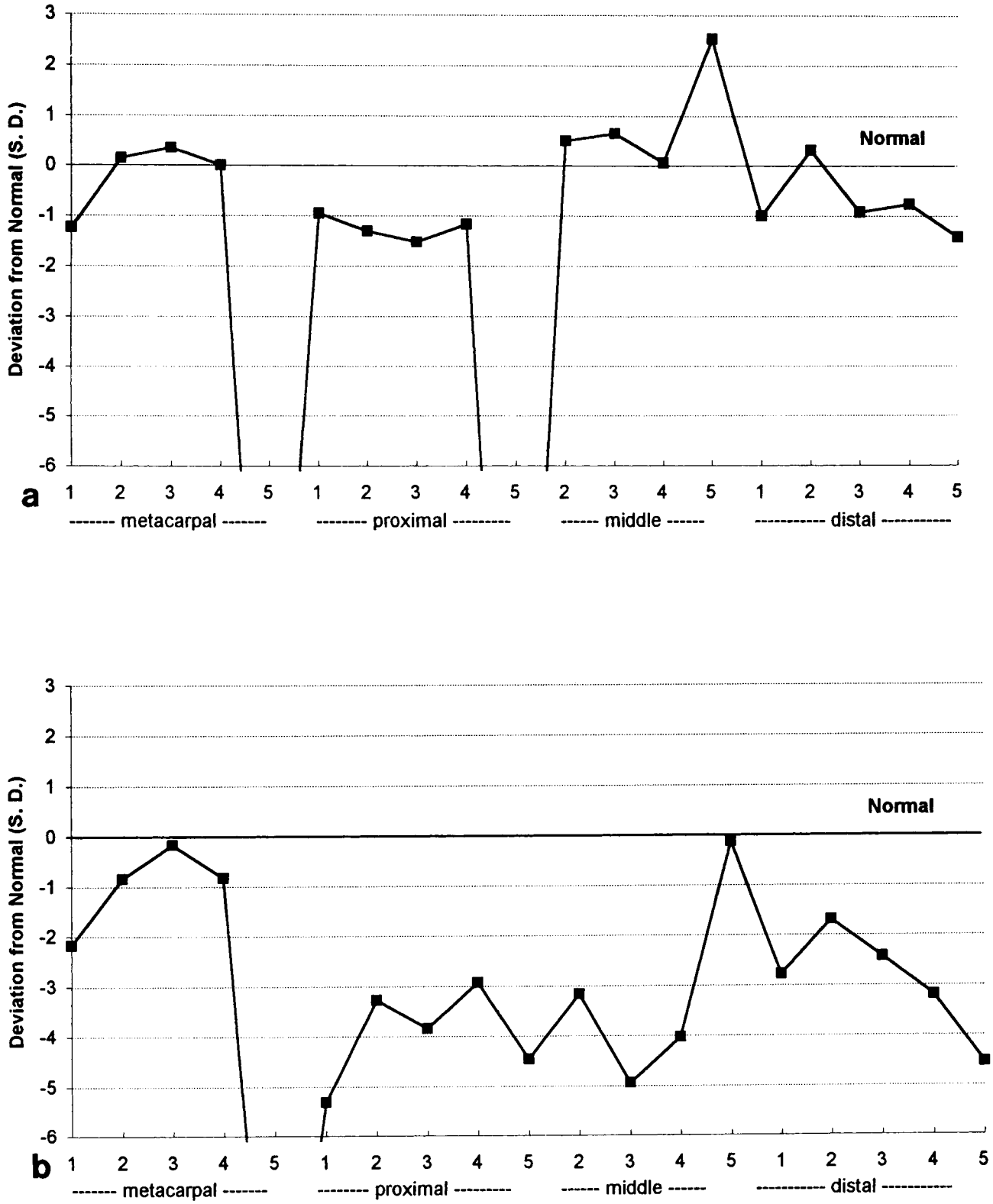

Fig. 3. Metacarpophalangeal pattern profiles of the girl's (**a**) and the boy's (**b**) left hand according to Poznanski et al. [1972].

TABLE I. Main Clinical Data Present in Patients With the Genée-Wiedemann Syndrome

	Sporadic cases from the literature, n = 19[b]	Familial cases from the literature, n = 16[b]	Present cases, n = 2	Summary familial cases, n = 18	Summary all cases, n = 37
Malar hypoplasia	17/17	7/7	2/2	9/9	26/26
Micrognathia	17/17	13/13	2/2	15/15	32/32
Antimongoloid slant	9/9	7/7	2/2	9/9	18/18
Scarce eyelashes	3/3	1/1	2/2	3/3	6/6
Lid ectropion	13/13	2/2	2/2	4/4	17/17
Coloboma of eyelid	5/6	3/3	0/2	3/5	8/11
Blepharophimosis	3/3	0/0	2/2	2/2	5/5
Conical teeth	0/0	0/0	2/2	2/2	2/3
Cleft palate	16/16	12/12	2/2	14/14	30/30
Ear anomalies	13/13	10/10	2/2	12/12	25/25
Deafness	4/4	2/2	0/2	2/4	6/8
CHD[a]	6/6	2/2	0/2	2/4	8/10
Extra nipples	5/7	2/2	1/2	3/4	8/11
Genital anomalies	4/5	2/2	1/2	3/4	7/9
Upper limbs					
Hypoplasia first ray	9/9	9/9	1/2	10/11	19/20
Hypoplasia fifth ray	19/19	16/16	2/2	18/18	37/37
Radial anomalies	14/14	7/7	1/2	8/9	22/23
Ulnar anomalies	14/14	7/7	1/2	8/9	22/23
Radio-ulnar synostosis	4/4	2/2	1/2	3/4	7/8
Carpal anomalies	4/4	2/2	2/2	4/4	8/8
Lower limbs					
Hypoplasia first ray	2/2	1/1	0/2	1/3	3/5
Hypoplasia fifth ray	16/16	15/15	2/2	17/17	33/33
Tibial anomalies	3/3	1/2	0/2	1/4	4/7
Fibular anomalies	3/3	1/2	0/2	1/4	4/7
Further radiolog. signs					
Spinal defects	4/4	2/3	0/2	2/5	6/9
Gender: Female	5	6	1	7	12
Male	13	10	1	11	24
Unknown	1	0	0	0	1

[a] Congenital heart defects (CHD) = VSD(6) ASD(2).
[b] References: Sporadic cases: Birch-Jensen [1949], Genée [1969], Wiedemann [1973], Pashayan and Feingold [1975], Wildervanck [1975], Smith and Jones [1975], Miller et al. [1979], Poissonnier et al. [1983], Meinecke and Rauskolb [1982], Donnai et al. [1987], Meinecke and Wiedemann [1987], Fryns and Van den Berghe [1988], Hauss-Albert and Passarge [1988], Chryzanowska et al. [1989], Barbuti et al. [1989], Vigneron et al. [1991]. Familial cases: Miller et al. [1979], Fineman [1981], Robinow et al. [1986], Meinecke and Wiedemann [1987], Opitz and Stickler [1987], Chryzanowska et al. [1989], Richieri-Costa and Guion-Almeida [1989], Robinow and Chen [1990], Ogilvy-Stuart and Parsons [1991], Gianotti et al. [1992], Pereira et al. [1992], Chryzanowska and Fryns [1993a].

order, a is the frequency of first-cousin marriages in the general population, and q is the frequency of the autosomal recessive gene. If q is small, as in the case of the Genée-Wiedemann syndrome this formula simplifies to $C = a/(a + 16q)$. Under the assumption of $q = 10^{-3}$ and of a frequency of first-cousin marriages in the general population of roughly 1/250 or 1/200, we would expect first-cousin marriages in the parents of cases to be 20% or 24%, respectively. In the whole series of cases only one very distantly related couple, fifth cousins with an inbreeding coefficient of 1/1.024, was observed [Widervanck, 1975].

Parent-to-Child Transmission

In the case of Robinow et al. [Robinow et al., 1986; Robinow and Chen, 1990], an affected mother had three normal and two affected children; there was no parental consanguinity. Given the extreme low frequency of the Genée-Wiedemann syndrome, such an observation is very unlikely.

Deviation of the Sex-Ratio

On one of the cases and on five of the healthy sibs the sex has not been reported. Taking all families with only one affected child there are 14 males and 7 females, taking all reported cases together there are 25 males and 14 females. However, none of these deviations is statistically significant at the 5% level, but nevertheless it is a remarkable deviation especially if one takes into account that the sex ratio in the healthy sibs is 1:1.

Testing for Recessive Inheritance

For a segregation analysis the method of ascertainment is a critical issue. We think that it is fair to assume that for all cases together the mode of ascertainment lies somewhere in between complete ascertainment, which means that every individual is ascertained regardless of whether there are any affected relatives or not and single incomplete ascertainment, which means that each family has been ascertained through only one affected individual irrespective of how

TABLE II. Neuropsychological Development in Cases of Genée-Wiedemann Syndrome

	Sporadic cases from the literature, n = 19[a]	Familial cases from the literature, n = 16[a]	Present cases, n = 2	Summary familial cases, n = 18	Summary all cases, n = 37
Normal	5/9	5/8	2/2	7/10	12/19
Slightly delayed	1/9	1/8[e]	0/2	1/10	2/19
Delayed due to physical problems	1/9[b]	2/8[f]	0/2	2/10	3/19
Severe mental retardation	2/9[c, d]	0/8	0/0	1/1	2/19

[a] References: given in Table I.
[b] Cerebral atrophy [Barbuti et al., 1989].
[c] Microcephaly [Hauss-Albert and Passarge, 1988].
[d] Slightly delayed at the age of 20 [Wiedemann, 1973].
[e] Normal at the age of 7 [Chryzanowska and Fryns, 1993b].
[f] Ogilvy-Stuart and Parsons [1991].

many affected others there may exist in the family, i.e., there is only one proposita per family. In case of the former the method of Li and Mantel [1968] provides an easy way of calculation; in case of the latter the formulas of Fisher [1934] can be used. The theoretical proportion is q = 0.25. Under the hypothesis of complete ascertainment we obtained in all families with the Genée-Wiedemann syndrome q = 0.44 (standard error of the estimate 0.094) and under the assumption of single incomplete ascertainment q = 0.3 (standard error of the estimate 0.084).

We note, that observations of similar irregularities were made, for example, in the TAR-syndrome, where 40 cases, some of them familial, with absence of consanguinity have been reported, the sex ratio was 14 males to 26 females, and there were fewer affected sibs than expected for an autosomal recessive trait [Hall et al., 1969]; later 3 cases of consanguinity were reported, at least two of these in communities where consanguinity is common [Shalev et al., 1983; Teufel et al., 1983; Ceballos-Quintal et al., 1992]. We think that the findings in the Genée-Wiedemann syndrome raise doubt about the mode of inheritance and may require an explanation.

ACKNOWLEDGMENTS

We thank Dr. C. Bassir, department of radiology of the Children's Hospital (KAVH), for his support and his helpful suggestions in conducting the metacarpophalangeal profile pattern.

REFERENCES

Allanson JE, McGillivray BC (1985): Familial clefting syndrome with ectropion and dental anomaly—without limb anomalies. Clin Genet 27:426–429.

Barbuti D, Orazi C, Reale A, Paradisi C (1989): Postaxial acrofacial dysostosis or Miller syndrome. Eur J Pediatr 148:445–446.

Birch-Jensen A (1949): Congenital deformities of the upper extremities. Domus Biologiae Hered. Humanae. Universitatis Hafniensis Vol 19, Odense. Andelsborgirykkeriet i Odense and det Danske Forlag.

Brunoni B, Guidugli-Neto J, Chedick ES, Borovic CD (1987): Acrofacial dysostosis: A new type? Rev Bras Genet 10:353–360.

Ceballos-Quintal JM, Pinto-Escalante D, Gongora-Biachi RA (1992): TAR-like syndrome in a consanguineous Mayan girl. Am J Med Genet 43:805–807.

Chrzanowska K, Fryns JP (1993a): Miller postaxial acrofacial dysostosis syndrome: Follow-up data of a family and conformation of autosomal recessive inheritance. Clin Genet 43:270.

Chrzanowska K, Fryns JP (1993b): Miller postaxial acrofacial dysostosis the phenotypic changes with age. Genetic Counseling 4: 131–133.

Chrzanowska K, Fryns JP, Krajewska-Walasek M, Wisniewski L, van den Berghe H (1989): Phenotype variability in the Miller acrofacial dysostosis syndrome: Report of two further patients. Clin Genet 35:157–160.

Dahlberg G (1947): "Mathematical Methods for Population Genetics." Basel: Karger.

Donai D, Hughes HE, Winter RM (1987): Postaxial acrofacial dysostosis syndrome in a sibship: Implications for genetic counselling. J Med Genet 24:422–425.

Fineman RM (1981): Recurrence of the postaxial acrofacial dysostosis syndrome in a sibship: Implications for genetic counselling. J Pediatr 98:87–88.

Fisher RA (1934): The effect of method of ascertainment upon the estimation of frequencies. Ann Eugen 6:13–25.

Fryns JP, van den Berghe H (1988): Acrofacial dysostosis with postaxial limb deficiency. Am J Med Genet 29:205–208.

Genée E (1969): Une forme extensive de dysostose mandibulo-faciale. J Genet Hum 17:45–52.

Giannotti A, Digilio MC, Virgili Q, Obregaon MG, Guadagni AM, Ventura T, Dallapiccola B (192): Familial postaxial acrofacial dysostosis syndrome. J Med Genet 29:752.

Gorlin RJ, Cohen MM, Levin LS (1990): "Syndromes of the Head and Neck." New York: Oxford University Press.

Hall JG, Levin J, Kuhn J, Ottenheimer EJ, van Berkum P, McKusick VA (1969): Thrombocytopenia with absent radius (TAR). Medicine 48:411–439.

Hauss-Albert H, Passarge E (1988): Postaxial acrofacial dysostosis syndrome with microcephaly, seizures and profound mental retardation. Am J Med Genet 31:701–703.

Li CC, Mantel N (1968): A simple method of estimating the segregation ratio under complete ascertainment. Am J Hum Genet 20:61–81.

Medeira A, Donnai D (1994): Postaxial acrofacial dysostosis syndrome with vertebral segmentation defects. Clinical Dysmorphol 3: 171–174.

Meinecke P, Rauskolb R (1982): Autosomal rezessive mandibulofaziale Dysostose mit Aplasie des 5. Strahls an Händen und Füßen. In Tolksdorf M, Spranger J (eds): "Klinische Genetik in der Pädiatrie", 3. Symposium in Kiel, 1981. Wissenschaftliche Information 8:445–450.

Meinecke P, Wiedemann HR (1987): Robin sequence and oligodactyly in mother and son: Probably a further example of the postaxial acrofacial dysostosis syndrome. Am J Med Genet 27:970–975.

Miller M, Fineman R, Smith DW (1979): Postaxial acrofacial dysostosis syndrome. J Pediatr 95:970–975.

Ogilvy-Stuart AI, Parsons AC (1991): Miller syndrome (Postaxial acrofacial dysostosis): Further evidence for autosomal recessive inheritance and expansion of the phenotype. J Med Genet 28: 695–700.

Opitz JM (1987): Editorial comment: Nager "Syndrome" versus "Anomaly" and its nosology with the postaxial acrofacial dysostosis syndrome of Genée and Wiedemann. Am J Med Genet 27:971–975.

Opitz JM, Stickler GM (1987): The Génée-Wiedemann syndrome, an acrofacial dysostosis: Further observation. Am J Med Genet 27:971–975.

Opitz JM, Mollica F, Sorge G, Milana G, Cimino G, Caltabiano M (1993): Acrofacial dysostoses: Review and report of a previously undescribed condition: The autosomal or X-linked dominant Catania form of acrofacial dysostosis. Am J Med Genet 47:660–678.

Pashayan H, Feingold M (1975): Case report 28, Patient 2. Synd Ident 3:9–10.

Pereira SCS, Rocha CMG, Guion-Almeida ML, Richieri-Costa A (1992): Postaxial acrofacial dysostosis: Report on two patients. Am J Med Genet 44:274–279.

Poissonier M, Neuville V, Petit Ph, Busuttil R (1983): Dysostose mandibulo-faciale et ulno-fibulaire léthale. Ann Pediatr 30: 713–717.

Poznanski AK (1974): "The Hand in Radiologic Diagnosis." Philadelphia: Saunders.

Poznanski AK, Garn SM, Nagy JM, Gall JC (1972): Metacarpophalangeal pattern profiles in the evaluation of skeletal malformations. Radiology 104:1–11.

Richards M (1987): Miller's syndrome: Anaesthetic management of postaxial acrofacial dysostosis. Anaesthesia 42:871–874.

Richieri-Costa A, Guion-Almeida ML (1989): Postaxial acrofacial dysostosis: Report of a Brazilian patient. Am J Med Genet 33: 447–449.

Robinow M, Chen H (1990): Genée-Wiedemann syndrome in a family. Am J Med Genet 37:293.

Robinow M, Johnson GF, Apesos J (1986): Robin sequence and oligodactyly in mother and son. Am J Med Genet 25:293–297.

Rodríguez JI, Palácios J (1990): Severe postaxial acrofacial dysostosis: An anatomic and angiographic study. Am J Med Genet 35:490–492.

Shalev E, Weiner E, Feldman E, Cohen H, Zuckerman H (1983): Micrognathia: Prenatal ultrasonographic diagnosis. Int J Gynaecol Obstet 21:343–345.

Smith DW, Jones KL (1975): Case Report 28, patient 1. Synd Ident 3:7–8.

Teufel M, Enders H, Dopfer R (1983): Consanguinity in a Turkish family with thrombocytopenia with absent radii (TAR) syndrome. Hum Genet 64:94–96.

Vigneron J, Stricker M, Vert P, Rousselot JM, Levy N (1991): Postaxial acrofacial dysostosis (Miller) syndrome: A new case. J Med Genet 28:636–638.

Wiedemann HR (1973): Missbildungs-Retardierungs-Syndrom mit Fehlen des 5. Strahl an Händen und Füßen, Gaumenspalte, dysplastischen Ohren und Augenlidern mit radioulnarer Synostose. Klin Pädiatr 185:181–186.

Wildervanck LS (1975): Case report 28, patient 3. Synd Ident 3:11–13.